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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/676,873	09/30/2003	John Chan	COTH-P01-002	7993

28120 7590 11/02/2005

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EXAMINER	
DEJONG, ERIC S	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 11/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/676,873	CHAN ET AL.	
	Examiner	Art Unit	
	Eric S. DeJong	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-68* is/are pending in the application.

4a) Of the above claim(s) *2,17-20,36-55 and 57-68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-16,21-35 and 56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 10/25/2004+ 8/15/2005
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Election/Restrictions

Applicant's election with traverse of Group I (claims 1-56), of species (A) (claims 1-35 and 56), sub-species (C) (claims 1, 3-16, 21-35, and 56) and species (H) in the reply filed on 08/08/2005 is acknowledged. The traversal is on the grounds that the separate groups and species are each closely related and would not present an undue burden of search of searched together. In regards to the second required species election requirement, applicants argument is found persuasive and, therefore, the second required species election has been withdrawn by the Examiner. Applicants argument is not found persuasive regarding the required restriction between Groups I and II, the first required species election, and the required sub-species election for the following reasons.

In regards to the required restriction between Groups I and II, applicants argue that Groups I and II are so closely related and they share the same common features would facilitate searching both groups at once. The relationship between the two groups was set forth in the previous restriction requirement wherein the two groups are related as process of making and product made (see page 2, line 12 through page 3, line 8 of the previous Office action, mailed 05/04/2005). In this discussion, it was established that the product may be made by other and materially different processes which therefore warrants a restriction between the two designated groups. Applicants arguments are not directed to the merits on which this restriction requirement is based and are therefore not found persuasive.

In regards the first species election, applicants argue that polypeptide and polypeptide complexes are closely related so that a search of all species together would not constitute an additional search burden. In response, the Examiner points out that the search required for species A, a polypeptide, involves a search drawn to tertiary structural elements involving amino acid residues of a spatially conserved catalytic motif. In contrast, the search required for species B, a polypeptide complex, necessarily involves consideration of quaternary structural features in a polypeptide complex which would not be included in the search for species A. Therefore, the search required for both species A and B would not be coextensive and thus present and undue burden of search.

In regards to the sub-species election, applicants argue that a recipient polypeptide that binds an extracellular signaling component and a recipient polypeptide that catalytically modifies a target are so closely related that a search of all sub-species together would not constitute an additional search burden. In response, the Examiner points out that the each of the identified sub-species (C) through (E) each involve distinct and separate polypeptide recipients. Further, each of the identified sub-species are drawn to polypeptide recipients having different structures and biological activities. Therefore, the search required for one sub-species would therefore not be coextensive with the search required for remaining sub-species and thus present an undue burden of search.

Therefore, the remaining election and restriction requirements identified above are still deemed proper and is therefore made FINAL.

Claims 2, 17-20, 36-55, and 57-68 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and/or species, there being no allowable generic or linking claim. Applicant timely traversed the restriction and election requirements in the reply filed on 08/08/2005.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. See for example the instant specification at page 7, line 1, page 60, line 9, and page 64, line 17. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and /or amino acid sequences set forth in CFR § 1.821(a)(1) and (a)(2). The Sequence Listing filed by applicants on 08/18/2004 is acknowledged, however this application fails to comply with the requirements of CFR § 1.821 through 1.825 because it lacks SEQ ID numbers cited along with each sequence in the specification or Figures. Applicants are also reminded that SEQ ID numbers are not required in the Figures per se, however, the corresponding SEQ ID numbers then are required in the Brief Description of the Drawings section in the specification. Applicants are given the same response time regarding this failure to comply as that set forth to respond to this office action. Failure to respond to this requirement may result in

abandonment of the instant application or a notice of a failure to fully respond to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 1, 3-16, 21-35, and 56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In In re Wands (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation." These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

In considering the factors for the instant claims:

a) In order to use the claimed invention one of skill in the art must be able to computationally modify a recipient polypeptide that binds a target by replacing an

identified set of amino acid residues within said polypeptide with an identified spatially conserved catalytic motif, such that the engineered polypeptide would retain both of said binding and catalytic activities. For reasons discussed below, there would be an unpredictable amount of experimentation required to practice the claimed invention.

b) The disclosure provides methods and procedures for carrying out the *in silico* modeling of a recipient polypeptide to contain a spatially conserved catalytic motif. The disclosure does not provide detailed guidance on how to reliably determine when such computationally modeled polypeptides will retain both said binding and catalytic activities in a "real-world" engineered polypeptide other than relying on a brute force method of synthesizing and testing each modeled polypeptide in a laboratory environment.

c) The disclosure provides examples of computationally identifying catalytic sites that are suitable for engineering into a similar geometric region identified in a recipient polypeptide. The instant disclosure does not provide working examples wherein the computationally identified catalytic site was actually engineered recipient protein in the "real-world" and further tested to confirm that the resultant engineered polypeptide maintained the expected catalytic and binding activities as modeled.

d) The nature of the invention, computationally engineering polypeptide structures to obtain a new catalytically active polypeptide from readily available polypeptide and motif structures, is extremely complex.

e) The prior art shows that predicted structures can be used only if very close homologs with known structures are available. A recent review of protein modeling and structure prediction provided by Ginalski et al. published on states:

> "Theoretically, it should be possible to deduce structure from sequence by accurate simulation of physical processes. We are very far from achieving this goal, and the methods of practical importance were traditionally based on the observation that proteins with similar sequences are structurally similar as well." (Ginalski et al., page 1874, column 1, line 15 through column 2, line 5)

and

> "Predicted protein structures can be used if very close homologs with known structure are available... Currently available structure prediction methods do not allow for high-quality predictions of the quaternary structure of protein complexes and for the prediction of interactions between proteins. Current benchmarks indicate that methods predicting interactions can be successful mainly in cases when structures exhibit minimal conformation changes upon complex formation. Substantial errors observed in predicted models go beyond the limits tolerated by such methods." (Ginalski et al., page 1887 column 1, line 45 through column 2, line 2).

Claim 1 recites the method steps "a) obtaining a spatial relationship for the amino acid residues of a spatially conserved motif; b) identifying a set of amino acid residues in the recipient polypeptide, wherein said set of residues have a geometric relationship matches the spatially conserved geometry of the catalytic motif". Independent claims 21 and 56 recite similar steps wherein a conserved geometric motif is engineered replace a geometrically matched set of amino acids in a recipient polypeptide. However, the instant claims do not recite any limitation requiring a high degree of homology between the catalytic motif and the replaced set of amino acids in a recipient polypeptide. In one embodiment, the catalytic domain engineered into a recipient polypeptide could interfere with the instantly claimed binding activity of said polypeptide. It is acknowledged that the

catalytic motif is modeled so as to replace a set of amino acids with matching, spatially conserved geometry, however this does not provide for a high degree of sequence homology or functional homology. Similarly, the instant claims do not address the issue of reliably predicting if the modeled engineered polypeptide will maintain the predicted fold, overall structure, and said catalytic and binding activities when produced in a real-world laboratory environment.

f) The skill of those in the art of polypeptide modeling and structure prediction is extremely high.

g) The predictability of structural characteristics from comparative structural and geometric features is identified in the prior art only when very close homologs are utilized in the investigation.

h) The claims are broad in that they are drawn to engineering a generic recipient polypeptide to contain a generic spatially conserved catalytic motif.

The skilled practitioner would first turn to the instant disclosure for guidance in using the claimed invention. However, the disclosure lacks any evidence or guidance on how to reliably predict when a engineered polypeptide will maintain the predicted fold, overall structure, and said catalytic and binding activities when produced in a real-world laboratory environment. As such, the skilled practitioner would turn to the prior art for such guidance, however the prior art does not shows only examples where predicted structures can be used only if very close homologs with known structures are available. Finally, said practitioner would turn to trial and error experimentation to determine if modeled structural characteristics for a given protein are present in empirically

determined real-world protein structures. Such amounts to undue experimentation.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

Claims 1, 3-16, 21-35, and 56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims are drawn to a method of engineering a motif into a polypeptide comprising the steps of obtaining a spatial relationship comprising a spatially conserved motif, identifying a set of amino acid residues in a recipient polypeptide, and substituting said spatially conserved motif into said recipient polypeptide. However, it is unclear from the instant claims whether the claimed method steps for engineering a recipient polypeptide include only computer embodiments wherein the engineered peptide is modeled entirely *in silico*, embodiments wherein an "real-world" peptide is engineered and produced in a biological laboratory, or embodiments involving *in silico* modeling techniques in combination with generating a real-world peptide.

For the purpose of continuing examination, the Examiner has construed that the instantly claimed methods are drawn to an *in silico* embodiment wherein the steps are performed by computational means alone.

Conclusion

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instrument Examiner, Tina Plunkett, whose telephone number is (571) 272-0549.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. DeJong whose telephone number is (571) 272-6099. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D. can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight

(EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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EDJ EDJ

JSB. Brusca 27 October 2005

JOHN S. BRUSCA, PH.D
PRIMARY EXAMINER